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(54) Title: NUCLEOSIDE COMPOUNDS AND USES THEREOF

(57) Abstract: Nucleoside analogs and their prodrug forms include a sugar moiety and a heterocyclic base moiety, wherein especially preferred sugar moieties include ribofuranose, and particularly preferred base moieties include diazole and triazole. Contemplated compounds may be employed in pharmaceutical compositions, which may be used to treat an infection, an infestation, a neoplasm, or an autoimmune disease. Further contemplated uses include immunomodulation, and particularly modulation of Type 1 and Type 2 cytokine expression.

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NUCLEOSIDE COMPOUNDS AND USES THEREOF

This application claims the benefit of U.S. provisional application number 60/189672, filed March 15, 2000 and U.S. utility application number 09/594,410, filed June 16, 2000, both of which are incorporated herein by reference in their entirety.

5 Field of the Invention

The field of the invention is nucleoside analogs.

Background of the Invention

RibavirinTM (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a nucleoside analog that has demonstrated efficacy in treating viral diseases both in monotherapy [see *e.g.*, Hall, C. B. *et al.*, Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. N. Engl. J. Med. (1983), 308, 1443-1447], and in combination therapy with interferon-alpha [Reichard, O. *et al.* Randomized, double blind, placebo controlled trial of interferon alpha 2B with and without ribavirin for chronic hepatitis C. Lancet (1998), 351, 83-87].

In addition to its well known role as a direct antiviral agent, RibavirinTM also exhibits immunomodulatory properties [Hultgren, C., *et al.*; The antiviral compound ribavirin modulates the T helper Type1/Type2 subset balance in hepatitis B and C virus-specific immune responses. J. Gen. Virol. (1998), 79, 2381-2391], which has been demonstrated *in vitro* by measuring Type 1 cytokine concentrations produced by activated T cells from both humans and mice [Tam, R., *et al.* Ribavirin polarizes human T cell responses towards a Type 1 cytokine profile. J. Hepatol. (1999), 30, 376-382]. Such immunomodulatory properties may advantageously be employed in treatments of various diseases.

However, RibavirinTM is also known to exhibit significant toxicity [see *e.g.*, Joksic, G. *et al.* Influence of RibavirinTM on the micronucleus formation and in vitro proliferation of human lymphocytes. Neoplasma (2000);47(5):283-7], and especially hematotoxicity [see *e.g.*, Jarvis, S., *et al.* Ribavirin uptake by human erythrocytes and the involvement of nitrobenzylthioinosine-sensitive (es)-nucleoside transporters. Br J Pharmacol (1998) Apr;123(8):1587-92], thereby substantially reducing its usefulness in long-term treatments and/or treatments in relatively high dosages.

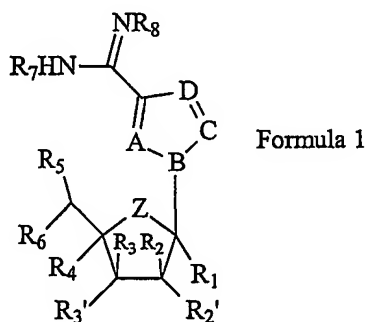
To reduce at least some of the cytotoxic effects of Ribavirin™, the L-isomer of Ribavirin™ (Levovirin) can be administered to a patient. For example, while oral administration of Ribavirin™ in rats at 180mg/kg over four weeks produced significant hemolytic anemia and leukopenia, Levovirin did not produce any observable clinical pathology. Administration of the L-isomer of Ribavirin™ reduces at least some aspects of cytotoxicity, however, conversion of Ribavirin™ into the corresponding L- isomer generally fails to improve target specificity with respect to a target cell and/or target organ.

Although various triazole-type nucleoside analogs for use in antiviral and antineoplastic treatments are known in the art, all or almost all of them suffer from one or more disadvantages. Therefore, there is still a need to provide methods and compositions for nucleosides with improved tolerability and specificity.

Summary of the Invention

The present invention is directed to nucleoside analogs and their corresponding prodrugs. Contemplated nucleoside analogs include a sugar moiety and a heterocyclic base moiety, and especially preferred sugar moieties include a ribofuranose. Particularly preferred base moieties include diazole and triazole.

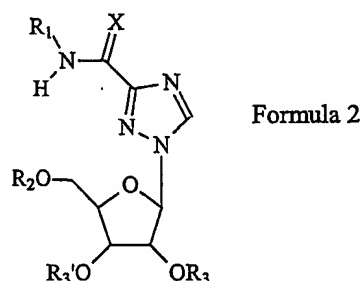
In one aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 1, in which the sugar is either in L- or D-configuration:



wherein A, C, and D are independently selected from N or C-R₉, and wherein R₉ is H, halogen, lower alkyl, alkenyl, alkynyl, amino, CN, SH, CHO, COOH, CH₂OH, vinyl halide or hydroxyl; B is N or C; Z is O, CH₂, or S; R₂' and R₃' are independently H, hydroxyl, protected hydroxyl, or halogen; R₁, R₂, R₃, R₄, R₅, are H, halogen, CN, CH₂OH, lower alkyl, vinyl, or acetylene, with the proviso that when R₂ is hydroxyl, then R₂' is not halogen, and with the further proviso that when

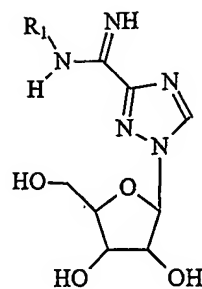
R_3 is hydroxyl, then R_3' is not halogen; R_6 is H, hydroxyl, protected hydroxyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{PO}(\text{OH})_2-$, an O-amino acid, O-retinoic acid, O-cholesterol, O-cholic acid, O-coumarinic acid, O-salicylic acid, O-succinic acid, an O-bile acid, an O-lipid, $\text{O-P}(\text{O})-(\text{O-CH}_2\text{-CH}_2\text{-S-CO-CH}_3)_2$, an O-steroid, an O-monophosphate derivative, an O-diphosphate derivative, or an O-triphosphate derivative; R_7 is H, alkyl, $\text{CH}_3\text{COO-}$, $\text{CH}_3\text{COO-Phenyl-CH}_2\text{-O-CO-}$, phenyl, $-(\text{CH}_2)_n\text{-COOH}$, coumarinic acid, salicylic acid, a dithiosuccinoyl derivative, a reductase cleavable group, phosphonoformic acid, or a phosphoramidate group; and R_8 is H, lower alkyl, phenyl, $\text{CH}_3\text{COO-}$, $\text{CH}_3\text{COO-Phenyl-CH}_2\text{-O-CO-}$, phenyl, or $-(\text{CH}_2)_n\text{-COOH}$; or R_7 and R_8 combined are selected from a cyclic structure or an amino acid, with the further proviso that (i) when R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , and R_8 are H, and when R_2' and R_3' are hydroxyl, then R_6 is not hydroxyl, and (ii) when R_1 , R_2 , R_3 , R_4 , R_5 , and R_8 are H, and when R_2' , R_3' , and R_6 are hydroxyl, then R_7 is not H.

In another aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 2, in which the sugar is either in L- or D-configuration:



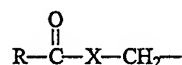
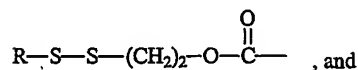
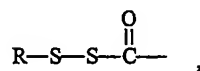
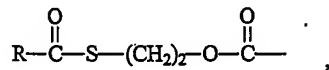
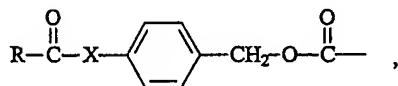
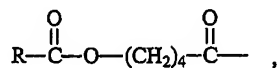
wherein X is O or NH; R_1 is a masking group of the amino group; R_2 is H, $-\text{CHO-}$, $-\text{C}(\text{O})\text{R}$, and $-\text{P}(\text{O})(\text{OR}')_2$, where R is $\text{C}_1\text{-C}_{17}$ alkyl, alkenyl, or alkynyl, and R' is a masking group of the phosphate group; and R_3 and R_3' are independently H or $\text{C}_1\text{-C}_{18}$ acyl, with the proviso that R_1 and R_2 are not hydrogen at the same time.

In a further aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 3, in which the sugar is either in L- or D-configuration:



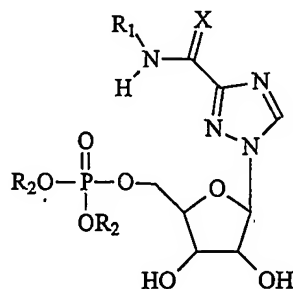
Formula 3

wherein R is a masking group selected from the group consisting of:



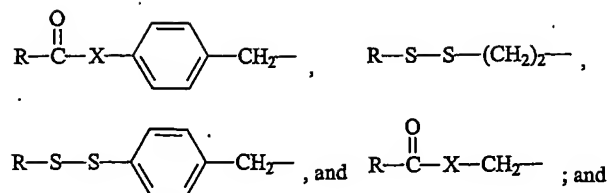
and wherein X is O or S, and R is a C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl.

- 5 In yet another aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 4, in which the sugar is either in L- or D-configuration:



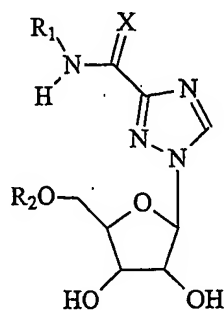
Formula 4

wherein R₁ is H or a masking group of the amino group; R₂ is a masking group of the phosphate selected from the group consisting of



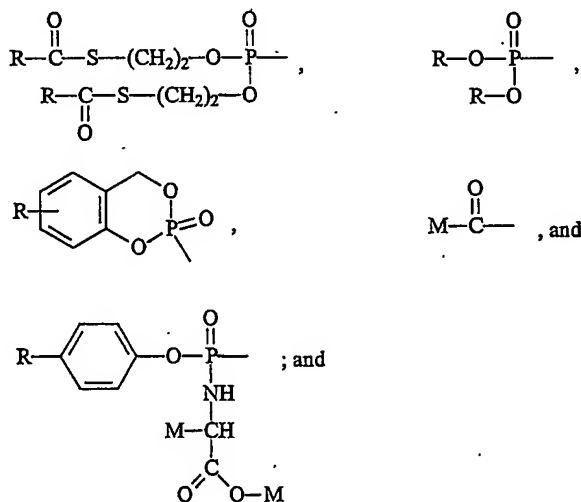
wherein X is O or S, and wherein R is C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl.

In a further aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 5, in which the sugar is either in L- or D-configuration:



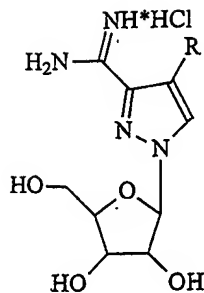
Formula 5

wherein R₁ is H or a masking group of the amino group, and wherein R₂ is a masking group of the phosphate having a structure selected from the group consisting of



wherein R is C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl, and wherein M is alkyl, alkenyl, alkynyl, aralkyl, aryl, or a hydrophobic group.

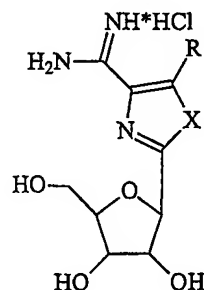
In another aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 6, in which the sugar is either in L- or D-configuration:



Formula 6

wherein R is hydrogen, hydroxy, halogen, alkyl, phenyl, vinyl, acetylene, an amide, or an amidine.

In yet another aspect of the inventive subject matter, the nucleoside analog has a structure according to formula 7, in which the sugar is either in L- or D-configuration:



Formula 7

wherein X is oxygen, sulphur, Se or NR, and wherein R is H, acetyl, or alkyl.

In yet further aspects of the inventive subject matter, a pharmaceutical composition comprises a therapeutically effective amount of any one or a combination of Formulas 1-7, or a pharmaceutically acceptable salt thereof admixed with at least one pharmaceutically acceptable carrier. Contemplated compositions are useful in treatment of various diseases, and particularly contemplated diseases include viral infections and cancer.

Detailed Description

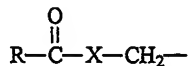
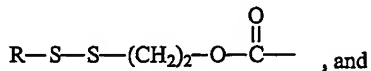
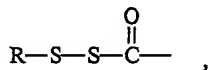
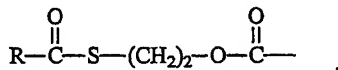
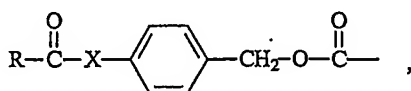
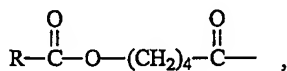
Where the following terms are used in this specification, they are used as defined below.

The terms "nucleoside" and "nucleoside analog" are used interchangeably, and refer to a compound comprising a sugar moiety covalently coupled to a heterocycle. Particularly preferred heterocycles include aromatic heterocycles, and even more preferred heterocycles include a purine, a pyrimidine, or a purine/pyrimidine analog. Most preferred heterocycles include a triazole. The term "nucleotide" refers to a nucleoside that is coupled to at least one phosphate group.

The term "heterocycle" refers to a carbocyclic radical having at least one heteroatom within the ring (e.g., N, O or S), wherein each position in the heterocycle may be independently substituted with a functional or non-functional group. Functional groups include nucleophilic groups, electrophilic groups, polar groups, (e.g., hydroxy, oxo, amino, imino groups), and nonfunctional groups include alkyl groups and halogens.

The term "protecting group" or "masking group" refers to a chemical group that is covalently bound to an oxygen or nitrogen atom of contemplated compounds to prevent further reaction of the oxygen or nitrogen atom in the course of derivatization of other functional groups in contemplated compounds. A wide variety of oxygen, phosphate, and nitrogen protecting groups are known to those skilled in the art of organic synthesis (see e.g., *Protecting Groups in Organic Synthesis* by James R. Hanson, Blackwell Science Inc; ISBN: 063204506X, or *Activating Agents and Protecting Groups, Handbook of Reagents for Organic Synthesis* by William R. Roush and Anthony J. Pearson; John Wiley & Son Ltd; ISBN: 0471979279, both incorporated by reference herein).

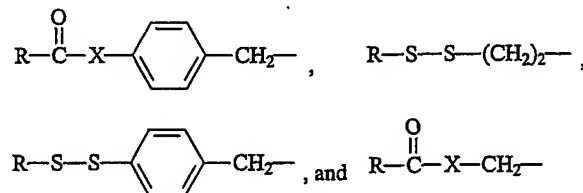
Particularly preferred masking groups of the amino group include groups having the following structures:



Further contemplated masking groups of the amino group include aliphatic ester-type masking groups (e.g., acetyloxypentanoic acid, acetyloxyhexanoic acid, or acetyloxypropanoic acid), para-acetyloxybenzyloxycarbonyl-type masking groups (e.g., para-hydroxybenzyloxy-

carbonyl, or para-acetyloxyxybenzloxycarbonyl), or para-acetyldisulfidecarbonyl-type masking groups.

Similarly, while various masking groups for the phosphate groups are suitable, particularly contemplated masking groups have the following structure:



However, in further alternative aspects, suitable masking groups may also include aliphatic ester-type masking groups (e.g., acetyloxypentanoic acid, acetyloxyhexanoic acid, or acetyloxypropanoic acid), para-acetyloxybenzloxycarbonyl-type masking groups (e.g., para-hydroxybenzloxycarbonyl, or para-acetyloxyxybenzloxycarbonyl), or para-acetyldisulfidecarbonyl-type masking groups.

The term "lower alkyl" refers to methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, i-butyl, or n-hexyl, and further includes a cyclic, branched or straight chain from one to six carbon atoms. The term "aryl" refers to an unsaturated aromatic carbocyclic radical having a single ring (e.g., phenyl) or two condensed rings (e.g., naphthyl), which may be substituted with a functional or non-functional group.

The term "L-nucleoside" refers to nucleoside compounds having a sugar moiety in L-configuration. Similarly, the term "D-nucleoside" refers to nucleoside compounds having a sugar moiety in D-configuration. The compounds of Formulas 1-7 may have multiple asymmetric centers. Accordingly, they may be prepared in either optically active form or as a racemic mixture. The scope of the invention as described and claimed encompasses the individual optical isomers and non-racemic mixtures thereof as well as the racemic forms of the compounds of Formulas 1-7. Similarly, the term " α " and " β " indicate the specific stereochemical configuration of a substituent at an asymmetric carbon atom in a chemical structure as drawn.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic and/or organic acid or base.

The terms "immunomodulatory" and "modulator" are herein used interchangeably and refer to natural or synthetic products capable of modifying the normal or aberrant immune system through stimulation or suppression. Particularly contemplated modulations include stimulation and/or inhibition of expression of cytokines, and it is even more particularly contemplated that modulation includes a change in the balance between Type 1 cytokines and Type 2 cytokines (e.g., a relative or absolute increase in Type 1 cytokines over Type 2 cytokines, a relative or absolute increase in Type 2 cytokines over Type 1 cytokines, or a suppression of both Type 1 and Type 2 cytokines).

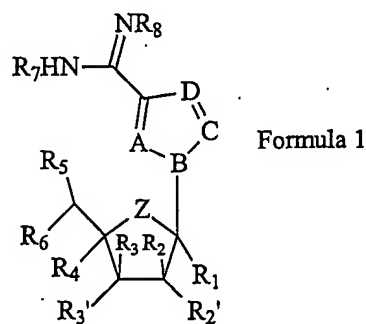
Contemplated compounds

The present invention is directed to nucleoside analogs and their corresponding prodrugs. In general, the following structure may broadly represent contemplated compounds:



where Nu is a nucleoside or nucleoside analog (preferably Levovirin or Viramidine) in which the sugar moiety is in D- or L-configuration, and wherein R (which may or may not be present) comprises a ligand or otherwise termed a substituent, that is designed to modify the nucleoside on the sugar, the base, or in some cases both the sugar and the base.

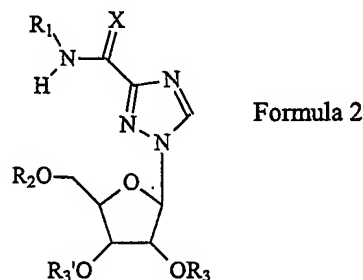
More particularly, contemplated nucleoside analogs have a structure according to formula 1, in which the sugar is either in L- or D-configuration:



wherein A, C, and D are independently selected from N or C-R₉, and wherein R₉ is H, halogen, lower alkyl, alkenyl, alkynyl, amino, CN, SH, CHO, COOH, CH₂OH, vinyl halide or hydroxyl; B is C or N; Z is O, CH₂, or S; R₂' and R₃' are independently H, hydroxyl, protected hydroxyl, or halogen; R₁, R₂, R₃, R₄, R₅, are H, halogen, CN, CH₂OH, lower alkyl, vinyl, or acetylene, with the proviso that when R₂ is hydroxyl, then R₂' is not halogen, and with the further proviso that when

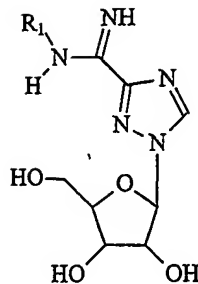
R_3 is hydroxyl, then R_3' is not halogen; R_6 is H, hydroxyl, protected hydroxyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{PO}(\text{OH})_2-$, an O-amino acid, O-retinoic acid, O-cholesterol, O-cholic acid, O-coumarinic acid, O-salicylic acid, O-succinic acid, an O-bile acid, an O-lipid, $\text{O-P}(\text{O})-(\text{O-CH}_2\text{-CH}_2\text{-S-CO-CH}_3)_2$, an O-steroid, an O-monophosphate derivative, an O-diphosphate derivative, or an O-triphosphate derivative; R_7 is H, alkyl, $\text{CH}_3\text{COO-}$, $\text{CH}_3\text{COO-Phenyl-CH}_2\text{-O-CO-}$, phenyl, $-(\text{CH}_2)_n\text{-COOH}$, coumarinic acid, salicylic acid, a dithiosuccinoyl derivative, a reductase cleavable group, phosphonoformic acid, or a phosphoramidate group; and R_8 is H, lower alkyl, phenyl, $\text{CH}_3\text{COO-}$, $\text{CH}_3\text{COO-Phenyl-CH}_2\text{-O-CO-}$, phenyl, or $-(\text{CH}_2)_n\text{-COOH}$; or R_7 and R_8 combined are selected from a cyclic structure or an amino acid, with the further proviso that (i) when R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , and R_8 are H, and when R_2' and R_3' are hydroxyl, then R_6 is not hydroxyl, and (ii) when R_1 , R_2 , R_3 , R_4 , R_5 , and R_8 are H, and when R_2' , R_3' , and R_6 are hydroxyl, then R_7 is not H.

Alternatively, and especially where it is desired that contemplated compounds include a triazole base moiety (e.g., the base of Ribavirin), contemplated nucleoside analogs have a structure according to formula 2, in which the sugar is either in L- or D-configuration:



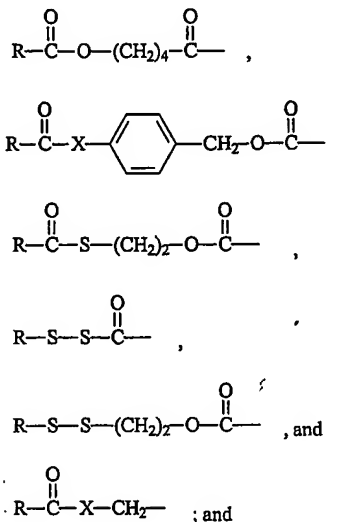
wherein X is O or NH; R_1 is a masking group of the amino group; R_2 is H, $-\text{CHO-}$, $-\text{C}(\text{O})\text{R}$, and $-\text{P}(\text{O})(\text{OR}')_2$, where R is $\text{C}_1\text{-C}_{17}$ alkyl, alkenyl, or alkynyl, and R' is a masking group of the phosphate group; and R_3 and R_3' are independently H or $\text{C}_1\text{-C}_{18}$ acyl, with the proviso that R_1 and R_2 are not hydrogen at the same time.

Moreover, where the nucleoside analogs of formula 2 have a carboxamidine moiety on the triazole base moiety, contemplated nucleoside analogs have a structure according to formula 3, in which the sugar is either in L- or D-configuration:



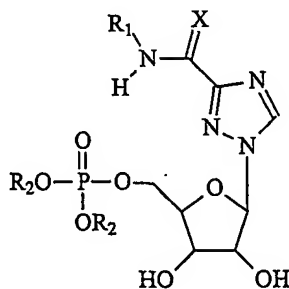
Formula 3

wherein R is a masking group selected from the group consisting of:



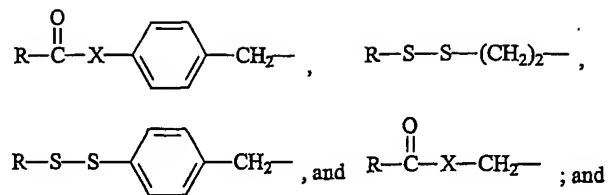
and wherein X is O or S, and R is a C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl.

- 5 In yet another aspect of the inventive subject matter, and especially where the nucleoside analogs have a phosphate group, contemplated nucleoside analogs have a structure according to formula 4, in which the sugar is either in L- or D-configuration:



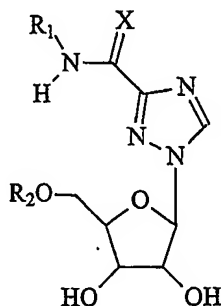
Formula 4

- 10 wherein R₁ is H or a masking group of the amino group; R₂ is a masking group of the phosphate selected from the group consisting of



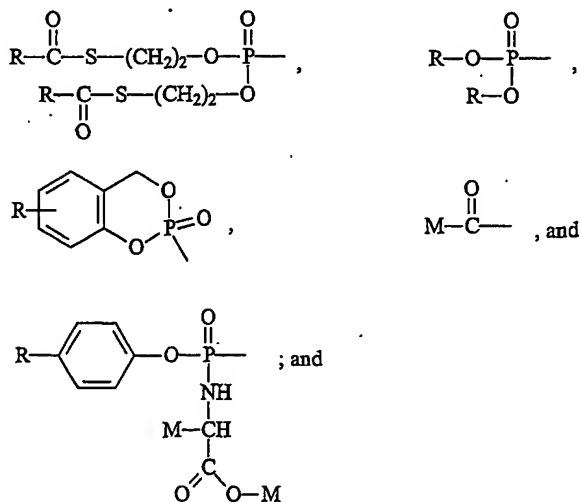
wherein X is O or S, and wherein R is C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl.

With respect to C_{5'}-substituents, and especially to phosphorous-containing C_{5'}-substituents, contemplated nucleoside analogs have a structure according to formula 5, in which
 5 the sugar is either in L- or D-configuration:



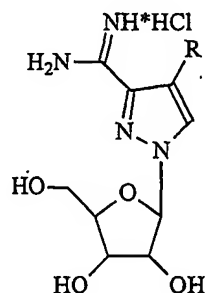
Formula 5

wherein R₁ is H or a masking group of the amino group, and wherein R₂ is a masking group of the phosphate having a structure selected from the group consisting of



10 wherein R is C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl, and wherein M is alkyl, alkenyl, alkynyl, aralkyl, aryl, or a hydrophobic group (*e.g.*, cholesterol or cholesterol derivative, bile acid or bile acid derivative, vitamin E, D, A, or K, steroids, etc).

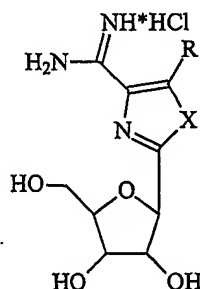
Alternatively, and especially where the triazole moiety is substituted with a diazole moiety, contemplated nucleoside analogs have a structure according to formula 6, in which the sugar is either in L- or D-configuration:



Formula 6

- 5 wherein R is hydrogen, hydroxy, halogen, alkyl, phenyl, vinyl, acetylene, an amide, or an amidine.

Moreover, contemplated nucleoside analogs may also include a modified diazole moiety and will generally have a structure according to formula 7, in which the sugar is either in L- or D-configuration:



Formula 7

10

wherein X is oxygen, sulphur, Se or NR, and wherein R is H, acetyl, or alkyl.

Uses of contemplated compounds

- 15 It is contemplated that compounds according to Formulae 1-7 may be used to treat a wide variety of conditions, and in fact any condition which responds positively to administration of one or more of such compounds. Among other things it is specifically contemplated that compounds according to the inventive subject matter may be used to treat an infection, an infestation, a cancer or tumor or an autoimmune disease. It is further contemplated that contemplated compounds may be used to target conditions or diseases in specific organs of a patient (typically a mammal, preferably a human), such as the liver or the heart.

Infections contemplated to be treated with the compounds of the present invention include respiratory syncytial virus (RSV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex type 1 and 2, herpes genitalis, herpes keratitis, herpes encephalitis, herpes zoster, human immunodeficiency virus (HIV), influenza A virus, hantann virus (hemorrhagic fever), human papilloma virus (HPV), measles, and fungus. Infestations contemplated to be treated with the compounds of the present invention include protozoan infestations, as well as helminth and other parasitic infestations.

Cancers or tumors contemplated to be treated include those caused by a virus, and the effect may involve inhibiting the transformation of virus-infected cells to a neoplastic state, inhibiting the spread of viruses from transformed cells to other normal cells and/or arresting the growth of virus-transformed cells. Autoimmune and other diseases contemplated to be treated include arthritis, psoriasis, bowel disease, juvenile diabetes, lupus, multiple sclerosis, gout and gouty arthritis, rheumatoid arthritis, rejection of transplantation, giant cell arteritis, allergy and asthma.

Consequently, a method of treating a mammal (preferably a human) having a cancer, a viral infection, an infestation, a cancer, or an autoimmune disease, comprises administering a therapeutically and/or prophylactically effective amount of a pharmaceutical containing a compound according to the inventive subject matter.

In yet another aspect, a method of treating a mammal (preferably a human) comprises administering a therapeutically and/or prophylactically effective amount of a pharmaceutical containing a compound of the present invention. In this aspect the effect may relate to modulation of some portion of the mammal's immune system, especially modulation of cytokine profiles of Type 1 and Type 2 with respect to one another. Where modulation of Type 1 and Type 2 cytokines occurs, it is contemplated that the modulation may include suppression of both Type 1 and Type 2, or reduction in expression of Type 1 cytokines and stimulation of expression of Type 2 cytokines.

In general, the most preferred uses according to the present invention are those in which the active compounds are relatively less cytotoxic to the non-target host cells and relatively more active against the target. In this respect, it is especially advantageous that contemplated L-nucleosides have increased stability over D-nucleosides, which could lead to better

pharmacokinetics. This result may attain because L-nucleosides may not be recognized by enzymes, and therefore may have longer half-lives.

It is further contemplated that compounds according to the present invention will be administered in any appropriate pharmaceutical formulation, and under any appropriate protocol.

5 Thus, administration may take place orally, parenterally (including subcutaneous injections, intravenous, intramuscularly, by intrasternal injection or infusion techniques), by inhalation spray, or rectally, topically and so forth, and in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles.

By way of example, it is contemplated that compounds according to the present
10 invention can be formulated in admixture with a pharmaceutically acceptable carrier. For example, the compounds of the present invention can be administered orally as pharmacologically acceptable salts. Because the compounds of the present invention are mostly water soluble, they can be administered intravenously in physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or
15 citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity. In particular, the modification of the present compounds to render them more soluble in water or other vehicle, for example, may be
20 easily accomplished by minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

Thus contemplated compounds are presented to a cell (or target cell) *in vivo* or *in vitro* in
25 a concentration range of between about 10nM to about 1mM, preferably between 100nM and 500μM, and most preferably between 5μM and 500μM. Where the administration of contemplated compounds is *in vitro*, admixing in any suitable form is contemplated. For example, where compounds according to the inventive subject matter are solid, admixing may be performed by adding the solid (*e.g.*, as powder or tablet) to the medium. Alternatively, where
30 contemplated are dissolved or are liquid, admixing may be done in a continuous or discontinuous form (*e.g.*, by pipetting). Similarly, where the administration of contemplated

compounds is *in vivo*, presentation of contemplated compounds is contemplated in any suitable form and/or formulation (*supra*). For example, where compounds according to the inventive subject matter are solid, a tablet may be presented to the patient. Alternatively, a solid may be dissolved and ingested by the patient, or where the compound is a liquid, contemplated

5 compounds or formulations comprising such compounds may be injected, ingested, or otherwise locally and/or systemically administered.

It should be particularly appreciated that a proper regimen of contemplated compounds *in vitro* and *in vivo* (including dosage, frequency, and route) can be established without undue experimentation by monitoring the desired biological effect. For example, where the biological
10 effect is an antiviral effect, virus load and/or propagation can be simply monitored by numerous methods well known in the art (*e.g.*, RT-PCR). In another example, where the desired effect is an immunomodulatory effect, change in the expression of Type 1 and/or Type 2 cytokines can be monitored via ELISA or other techniques well known to the person of ordinary skill in the art.

15 Moreover, combination therapies with administration of at least one of the contemplated compounds and at least one other pharmaceutically active ingredient are also contemplated. The contemplated compound and the pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order.

20 Examples of other drugs or active ingredients contemplated to be effective in combination with a modulator selected from Formula 1 or Formula 2 are anti-viral agents such as interferon, including but not limited to interferon α and γ , ribavirin, acyclovir, and AZTTM; anti-fungal agents such as tolnaftate, FungizoneTM, LotriminTM, MycelexTM, Nystatin and Amphotericin; anti-parasitics such as MintezolTM, NiclocideTM, VermoxTM, and FlagylTM, bowel
25 agents such as ImmodiumTM, LomotilTM and PhazymeTM; anti-tumor agents such as interferon α and γ , AdriamycinTM, CytosanTM, ImuranTM, Methotrexate, MithracinTM, TiazofurinTM, TaxolTM; dermatologic agents such as AclovateTM, CyclocortTM, DenorexTM, FloroneTM, OxisoralenTM, coal tar and salicylic acid; migraine preparations such as ergotamine compounds; steroids and immunosuppressants not listed above, including cyclosporins, DiprosoneTM,
30 hydrocortisone; FloronTM, LidexTM, TopicortTM and ValisoneTM; and metabolic agents such as insulin, and other drugs which may not nicely fit into the above categories, including cytokines

such as IL2, IL4, IL6, IL8, IL10 and IL12. Especially preferred primary drugs are AZT, 3TC, 8-substituted guanosine analogs, 2,3-dideoxynucleosides, interleukin II, interferons such as α B-interferons, tucaresol, levamisole, isoprinosine and cyclolignans.

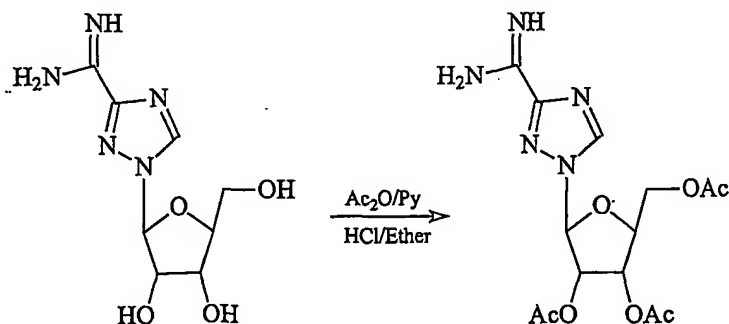
Particularly contemplated examples of therapeutic agents include agents that are effective for the modulation of immune system or associated conditions such as AZT, 3TC, 8-substituted guanosine analogs, 2', 3'-dideoxynucleosides, interleukin II, interferons, such as α -interferon, tucaresol, levamisole, isoprinosine and cyclolignans. Certain compounds according to the present invention may be effective for enhancing the biological activity of certain agents according to the present invention by reducing the metabolism or inactivation of other compounds and as such, are co-administered for this intended effect.

Still other contemplated uses of the compounds include use as intermediates in the chemical synthesis of other nucleoside or nucleotide analogs that are, in turn, useful as therapeutic agents or for other purposes.

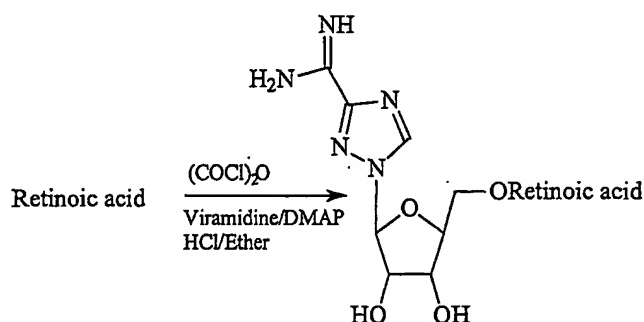
Synthesis of contemplated compounds

The following synthetic schemes provide exemplary synthetic routes for the formation of contemplated compounds, in which Levovirin and Viramidine (in both D- and L-configuration) may interchangeably be employed, and wherein Levovirin and/or Viramidine may further comprise additional substituents and/or ligands.

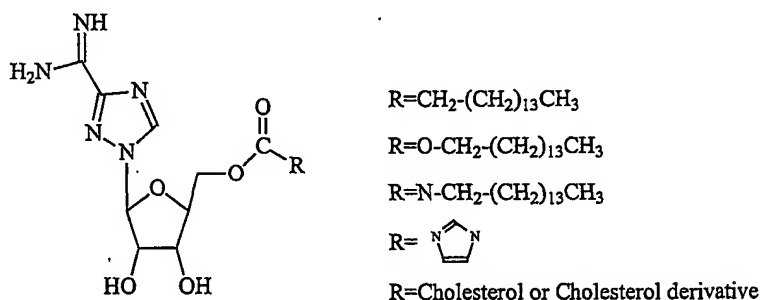
An exemplary synthetic scheme for acylated contemplated compounds (here: tri-O-acetylated, which may or may not be modified with a masking group of the amino group) is depicted below.



Alternatively, a 5'-retinoyl derivative of contemplated compounds (which may be modified with a masking group of the amino group) is prepared according to the following scheme.

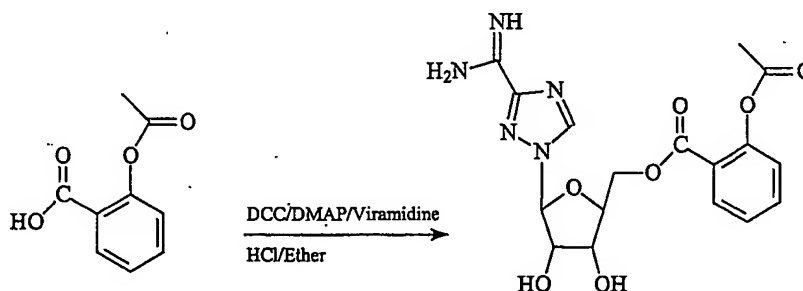


- 5 The following further 5'-derivatives of contemplated compounds may be prepared in a procedure similar to that described in C. Sergheraert, C. Pierlot, A. Tartar, Y. Henin, M. Lemaitre, *J. Med. Chem.*, 36, 826-830, 1993.

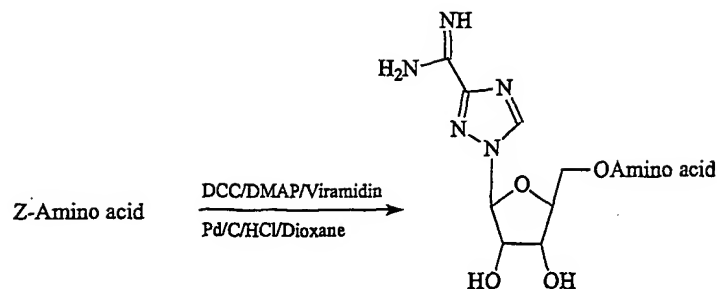


Other groups for R include bile acids, lipids, cholic acid, and vitamins.

- 10 A salicylic acid-based prodrug of contemplated compounds may be obtained as follows:

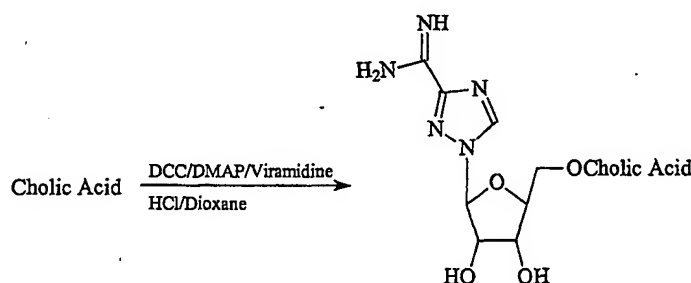


Similarly, 5'-amino acid ester derivatives (in which at least one of the 2'- and 3'-hydroxyl, or the carboxamidine group may further be modified) may be prepared as shown below:

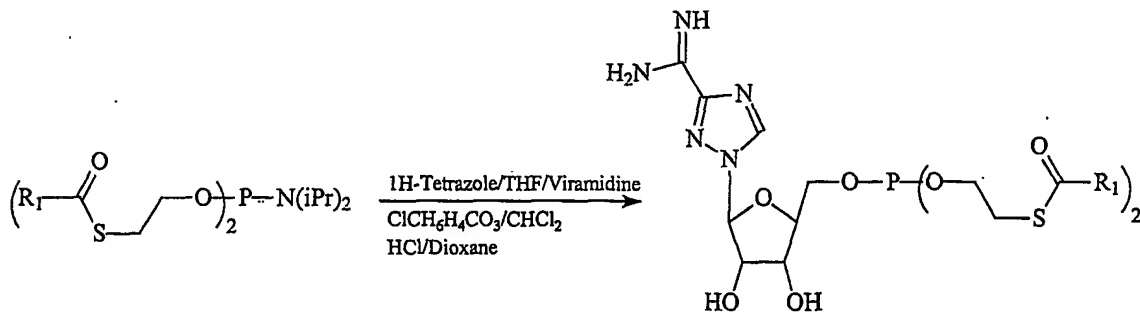


Where specific delivery of contemplated compounds to the liver and the biliary system is desired, targeting of the endogenous bile acid transport system is an attractive candidate.

Consequently, bile acid (or cholic acid) conjugates of contemplated compounds (in which at least one of the 2'- and 3'-hydroxyl, or the carboxamidine group may further be modified) are especially contemplated and their synthesis may be accomplished as represented below:

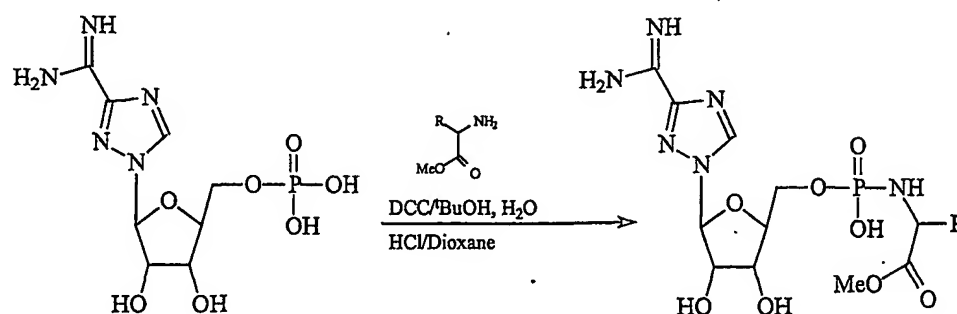


Preparation of protected 5'-monophosphate derivatives are shown below. It is especially contemplated that protecting the negative charges of one or more phosphate groups with neutral substituents may form more lipophilic derivatives, which are expected to revert back to the corresponding phosphates once inside a cell.

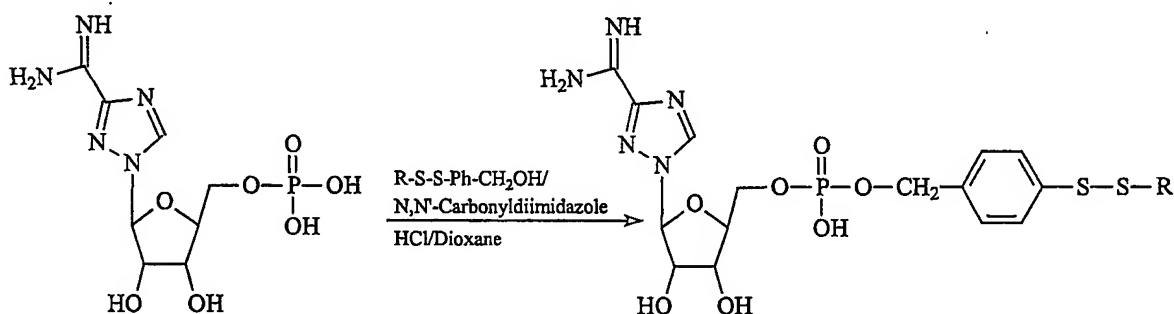


wherein R_1 includes alkyl groups such as $\text{CH}_3\text{C(O)S-CH}_2\text{CH}_2-$; $(\text{CH}_3)_2\text{CHC(O)S-CH}_2\text{CH}_2-$; $(\text{CH}_3)_3\text{CC(O)S-CH}_2\text{CH}_2-$; $(\text{CH}_3)_3\text{CC(O)OCH}_2-$; $\text{C}_6\text{H}_5\text{C(O)S-CH}_2\text{CH}_2-$ or $\text{HOCH}_2\text{CH}_2\text{SS-CH}_2\text{CH}_2-$.

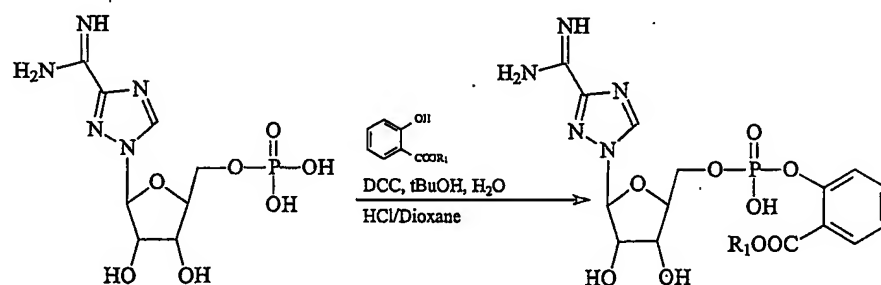
Amino acid phosphoramidates are yet another class of contemplated prodrugs that may be synthesized as described below:



wherein R includes alkyl, alkenyl, aryl, or alkaryl, all of which may further include one or more functional groups or substituents. Still further contemplated monophosphate prodrug forms of contemplated compounds are shown below:

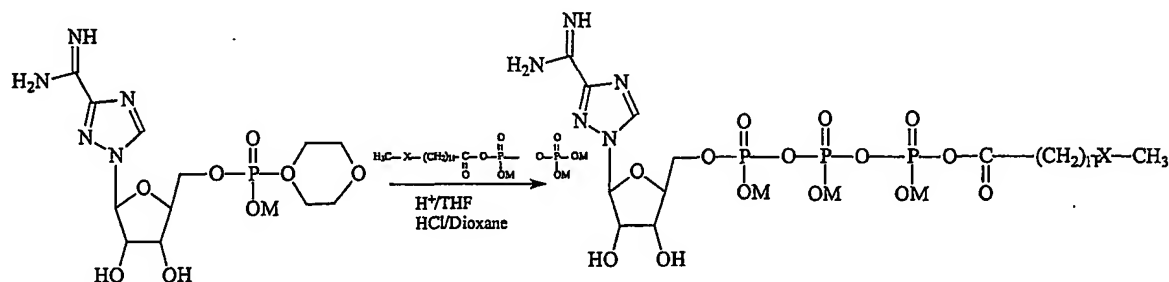


Salicylate-based nucleotide prodrugs of contemplated compounds may be obtained as follows:



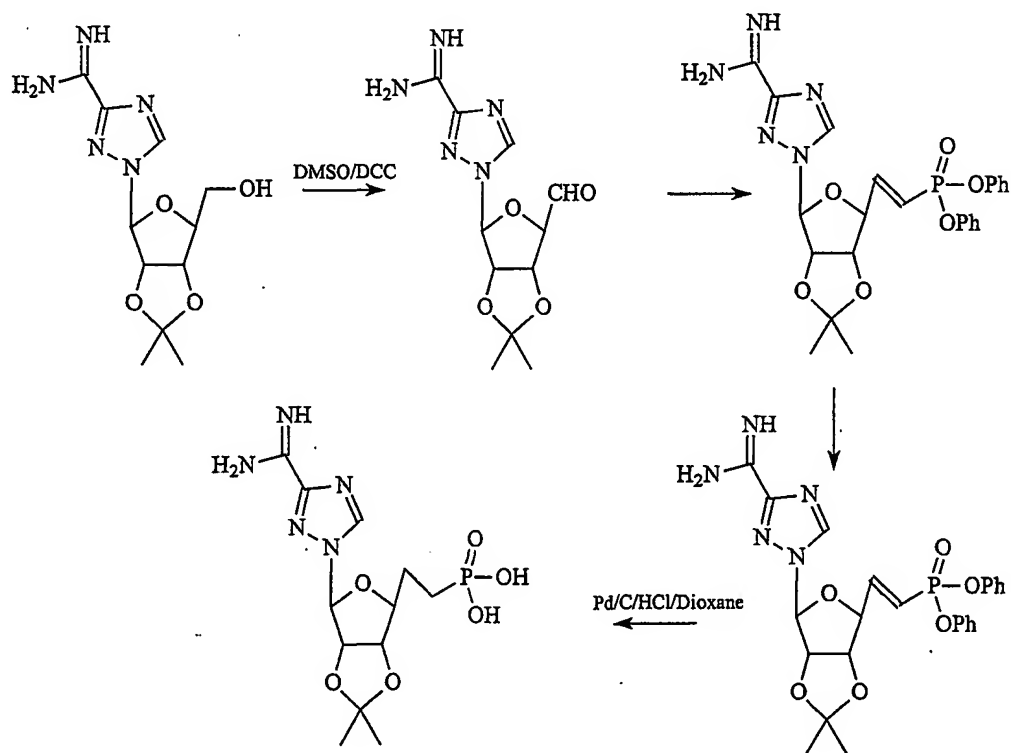
wherein R_1 may be CH_3 , Phenyl, H, or a sugar moiety (e.g., glucopyranose). It should further be appreciated that contemplated prodrug forms also include diphosphate and triphosphate forms, which may bypass one or more metabolic steps within a cell.

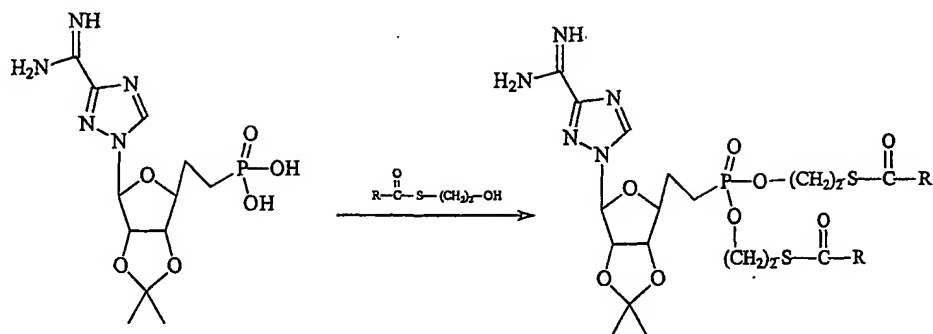
The following examples illustrate lipophilic nucleotide prodrugs, which may be prepared as depicted below (and wherein at least one of the 2' and 3'-OH groups and/or the carboxamidine group may further be protected/modified):



5 in which X is O or CH₂, and M is NBU₄⁺.

Phosphonate prodrugs of contemplated compounds (in which at least one of the 2' and 3'-OH groups and/or the carboxamidine group may further be protected/modified) may be prepared following a procedure as outlined below:

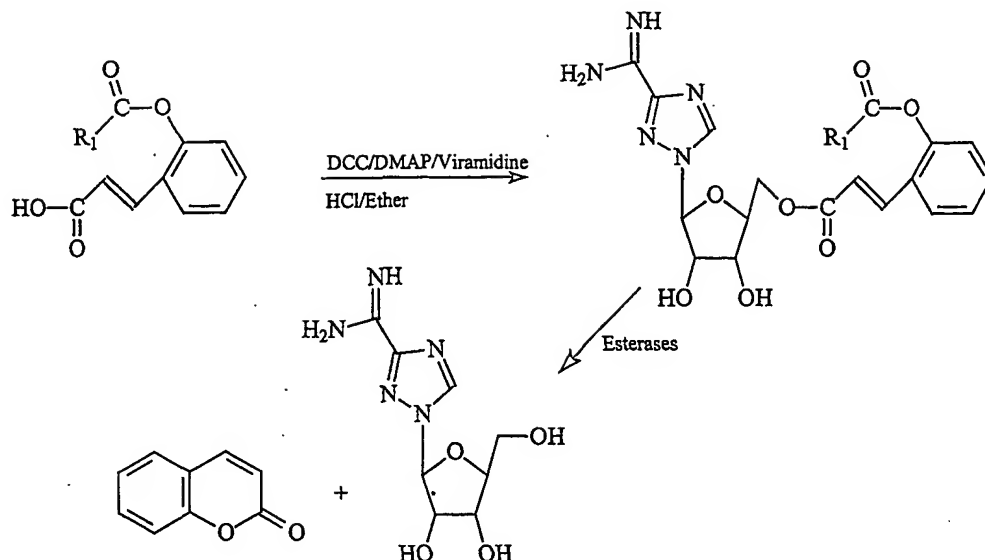




Other possible prodrugs of contemplated compounds include the combinations of the groups shown in PCT patent application WO 98/39342, WO 98/39343, WO 98/39344 and WO 99/45016.

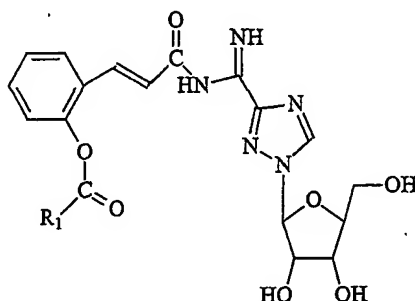
- 5 It is still further preferred that where contemplated compounds are orally administered, that such compounds will substantially remain unchanged (*i.e.*, more than 75%, preferably more than 85%, and most preferably more than 95% remain unchanged) during the passage through the intestinal tract, and it is even more preferred that such compounds will be transported (actively or passively) across the intestinal wall, and finally, once in the systemic circulation,
- 10 will be converted back to the parent nucleoside or nucleotide. Consequently, enzyme activated prodrugs are especially contemplated and particularly preferred enzymes include intracellular and extracellular esterases, enzymes with disulfide reductase activity, and ras-Farnesyl protein transferase activated prodrugs.

- For example, contemplated prodrugs include coumarin-based prodrugs, salicylate based
- 15 prodrugs, dithiosuccinoyl (Dts)-based prodrugs, reductase mediated prodrugs, 4-acyloxybenzyl-oxycarbonyl-based prodrugs, ras-farnesyl protein transferase prodrugs, succinic acid based prodrugs, and homoserine-based prodrugs:



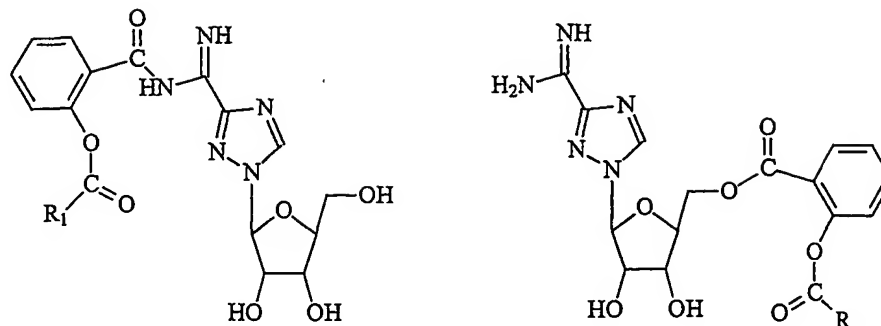
Such coumarin-based prodrugs are easily cleaved by esterases, which is followed by lactonization, thereby releasing contemplated compounds. R_1 may be CH_3 , fatty acids, cholesterol, cholic acids, or bile acids. Alternatively, coumarinic acid may be used to mask the

5 carboxamidine function of contemplated compounds to produce the following prodrug:

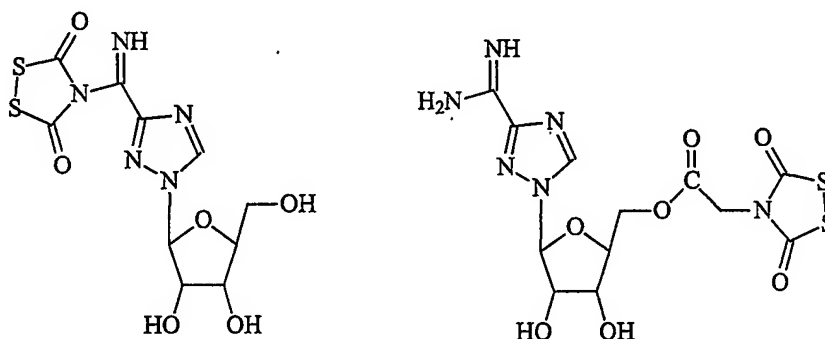


Similarly, it is contemplated that salicylate-based prodrugs may include an activation step that includes a neighboring group catalysis mechanism. Both hydroxyl and amide masked salicylates of Levovirin are shown below, and it is contemplated that their synthesis will

10 substantially follow the synthetic scheme shown above for coumarinic acid by substituting salicylic acid for coumarinic acid. R_1 may be CH_3 , fatty acids, cholesterol, cholic acids, and bile acids.

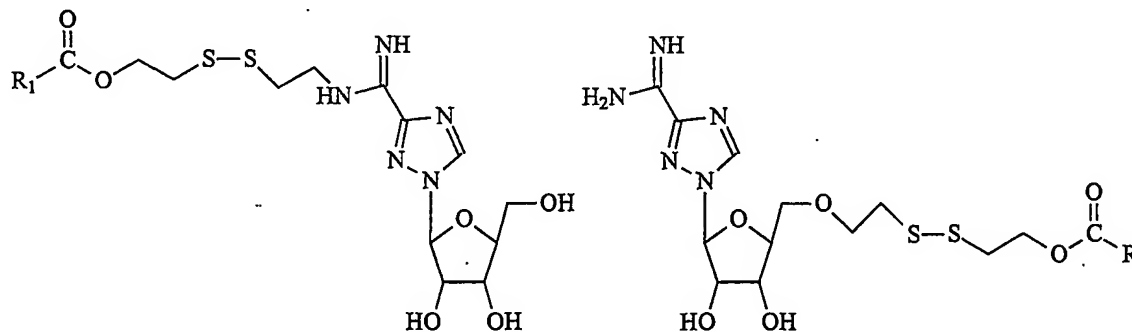


Where disulfide-reductase activated prodrugs are preferred, dithiosuccinoyl (Dts)-based prodrug forms may be synthesized, which will result in the corresponding nucleoside by enzyme-activated reduction (which may further include esterase action).

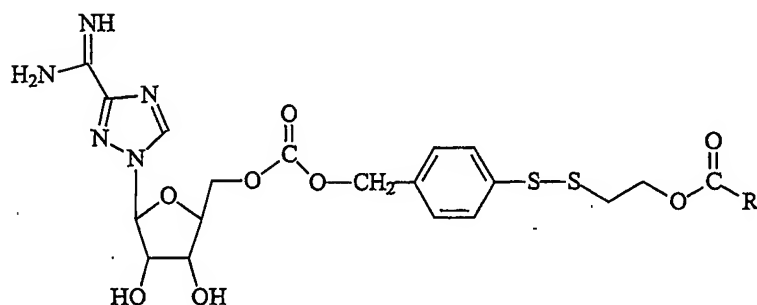
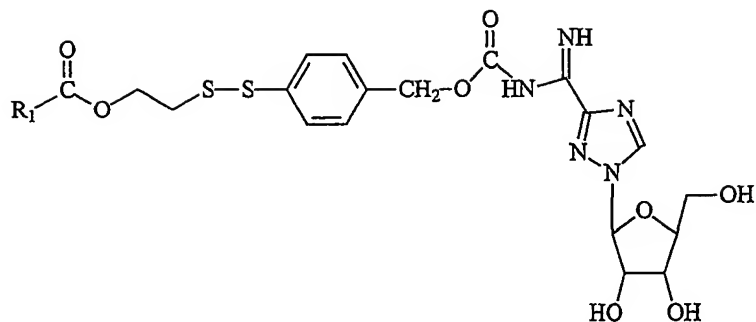


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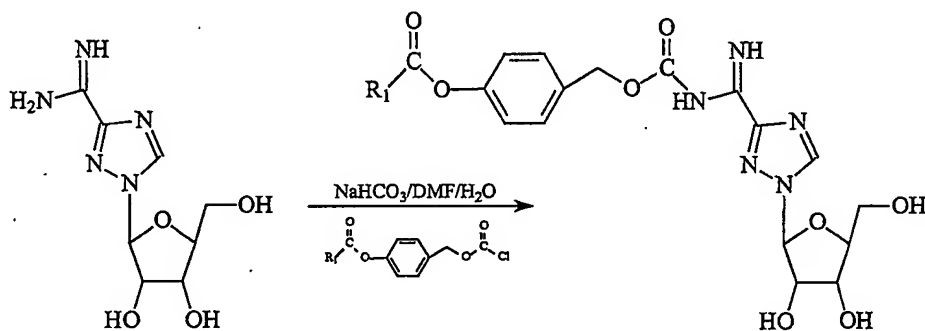
Further contemplated reductase-mediated prodrugs are cleaved by a combination of esterases and reductases and are contemplated to yield the corresponding nucleoside, and exemplary prodrugs are depicted below in which R₁ may be CH₃, fatty acids, cholesterol, cholic acids, and bile acids.



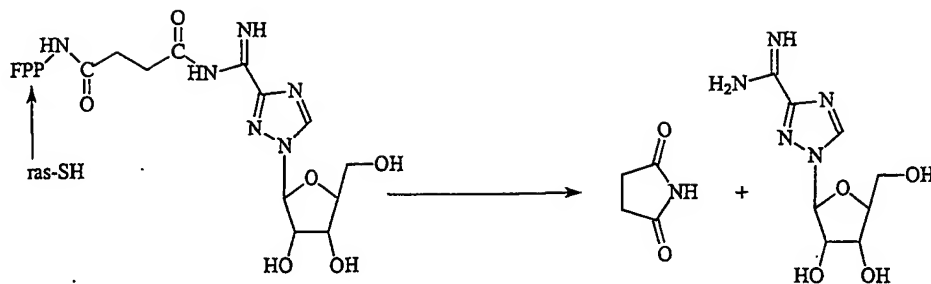
10



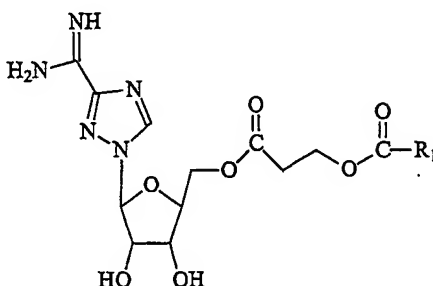
4-Acyloxybenzyloxycarbonyl-based prodrugs may be prepared by using the protecting group strategy used to block amino group of any amino acids and is represented in the scheme below. These prodrugs are cleaved by esterases giving back the free nucleoside. R_1 may be CH_3 , fatty acids, cholesterol, cholic acids, and bile acids.



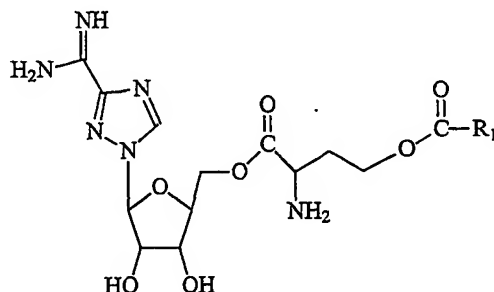
Ras-Farnesyl protein transferase activated prodrugs may be especially advantageous where tumor cells or tumor masses are targeted, and exemplary prodrugs of this type are represented below.



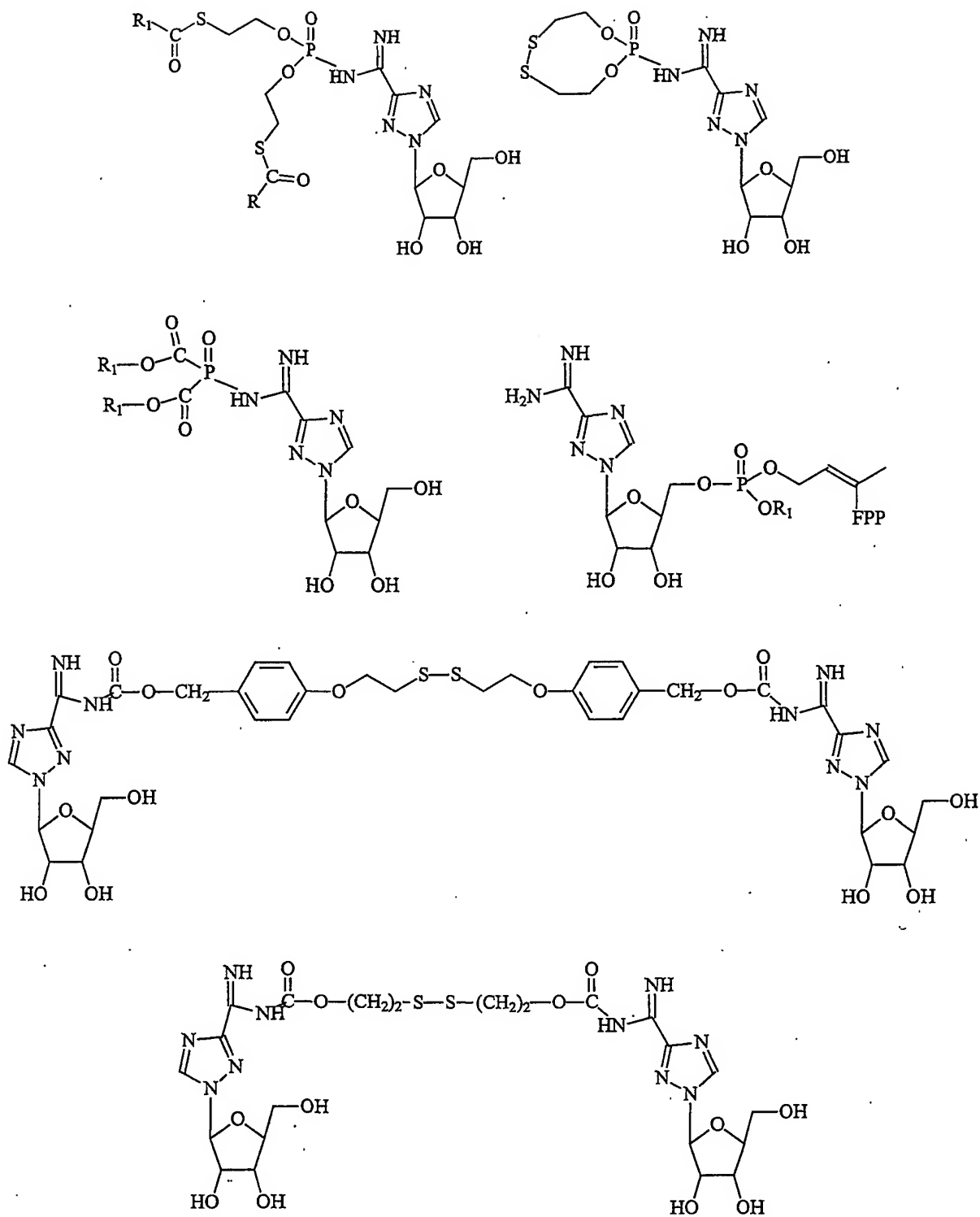
Succinic acid based prodrugs are represented by the following structure, wherein R_1 is CH_3 , fatty acids, cholesterol, cholic acids, or bile acids.



- 5 Similarly, homoserine-based prodrugs may be prepared from Levovirin, and such prodrugs are depicted below, in which R_1 is CH_3 , fatty acids, cholesterol, cholic acids, or bile acids.



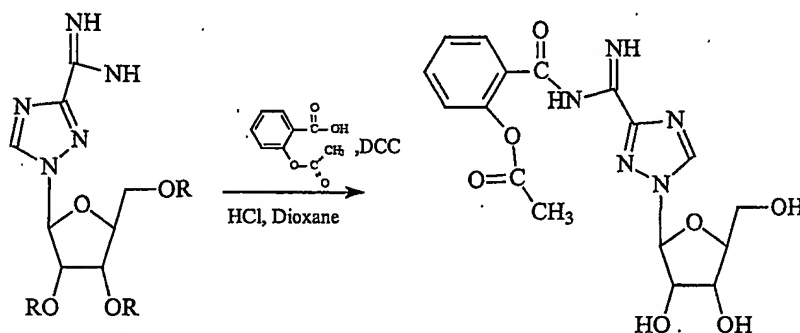
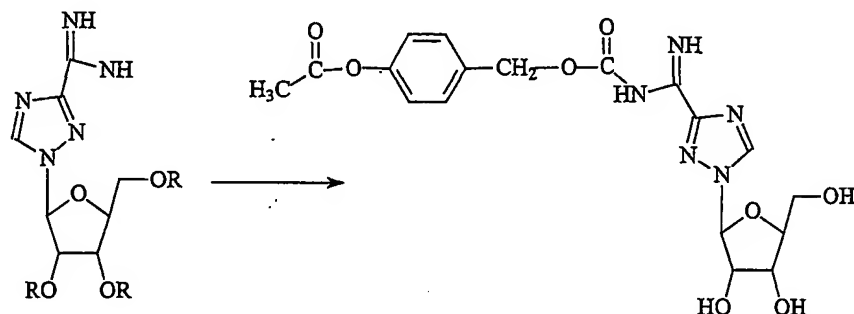
- In still further contemplated aspects of the inventive subject matter, phosphoramidate based nucleosides and nucleotides, phosphonoformic acid based nucleosides and nucleotides, nucleoside and nucleotide dimers, and further ras-farnesyl protein transferase activated prodrugs are contemplated, and exemplary structures are as depicted below (in which R_1 may be CH_3 , fatty acids, cholesterol, cholic acids, or bile acids):
- 10



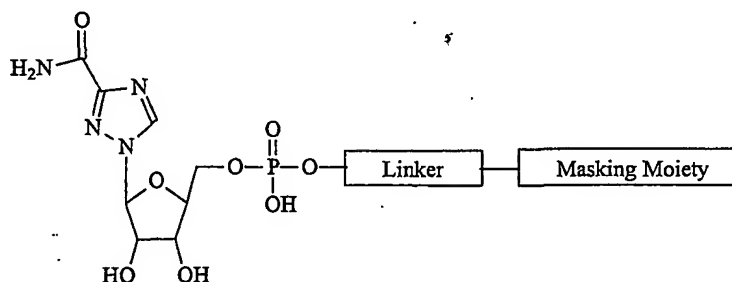
5

It should still further be appreciated that all of contemplated prodrugs may be synthesized in their respective mono-, di- and triphosphate form, and their respective phosphonate forms.

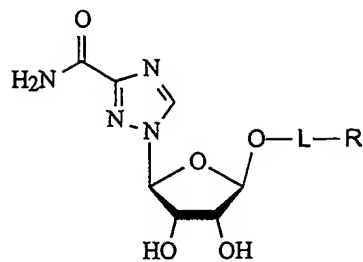
In still further contemplated aspects of the inventive subject matter, contemplated compounds may be obtained by derivatizing the amide or amidine function of a carboxamide or carboxamidine group. The following examples illustrate exemplary amino-modified prodrug forms of Viramidine:



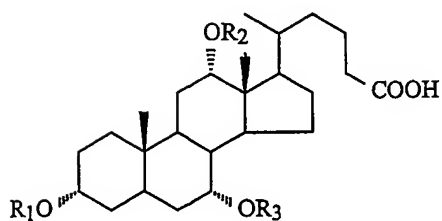
An additional contemplated example of the formation of contemplated prodrugs is depicted below, in which the linker may comprise ligands such as lipids, alkyl groups, bile acid, and vitamins, and wherein the masking moiety is covalently coupled to the linker:



For example, particularly contemplated linkers include alkyl, cholesterol, bile acid, various lipids and lipid soluble vitamins (*e.g.*, A, D, E, K), and exemplary prodrug forms of Levovirin are outlined below:

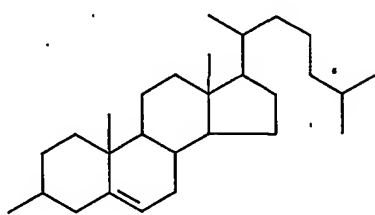


R = Alkyl, Cholesterol, Bile acid, Fat soluble vitamin, or other lipids
 L = -C(O)- or -OOCCH₂CH₂CO

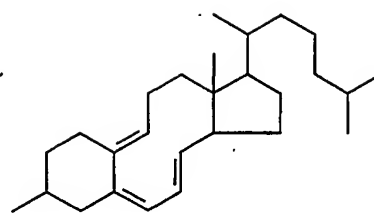


R₁ = R₂ = R₃ = H or Ac

Derivatives of cholic acid

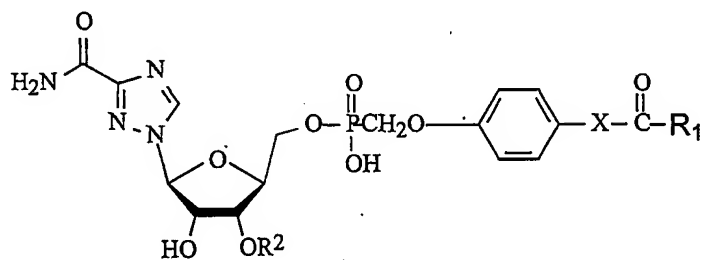


Cholesterol derivative



Vitamin D derivative

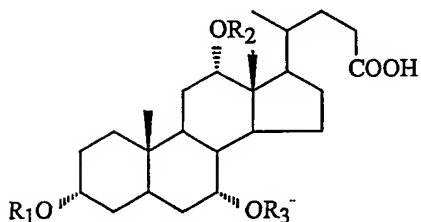
Alternatively, Levovirin phosphonate prodrugs may have structures as outlined below:



X = O, S

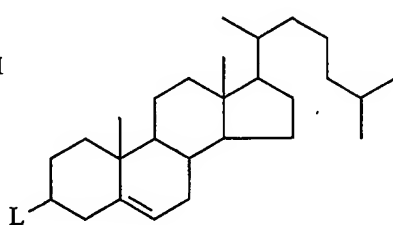
R² = H, Ac

R₁ = Alkyl, lipids, bile acids, fat soluble vitamin, etc.



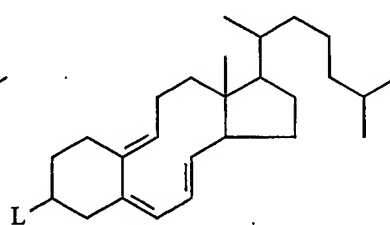
R₁ = R₂ = R₃ = H or Ac

Bile acid or derivatives



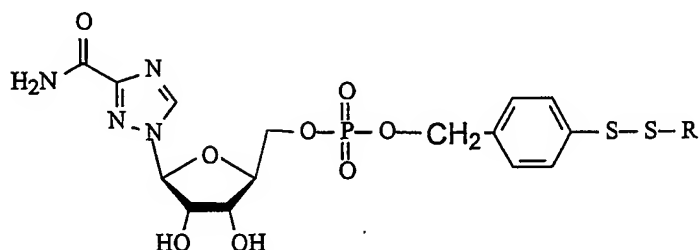
L = HOOCCH₂CH₂COO

Cholesterol derivative

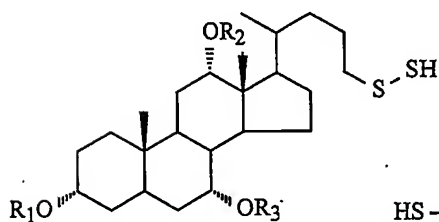


Vitamin D derivative

In still further alternative aspects, Levovirin monophosphate prodrugs may have structures as follows:

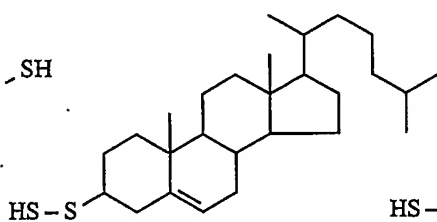


R = Alkyl, Cholesterol, Bile acid, Fat soluble vitamin, or other lipids

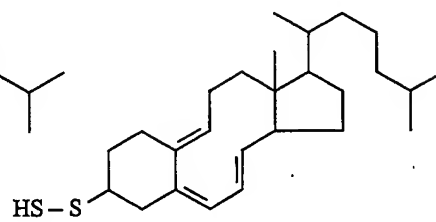


R₁ = R₂ = R₃ = H or Ac

Derivatives of cholic acid

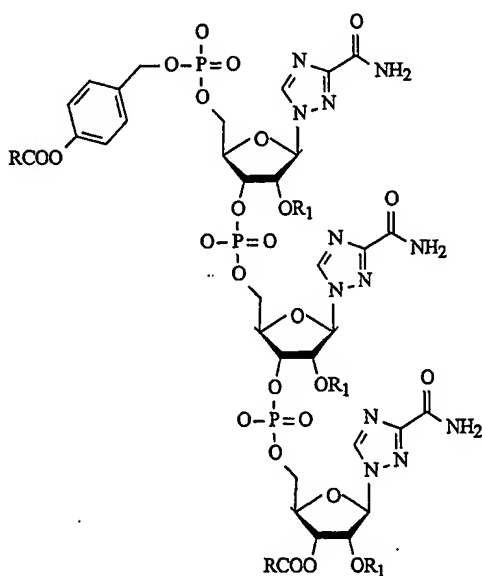


Cholesterol derivative

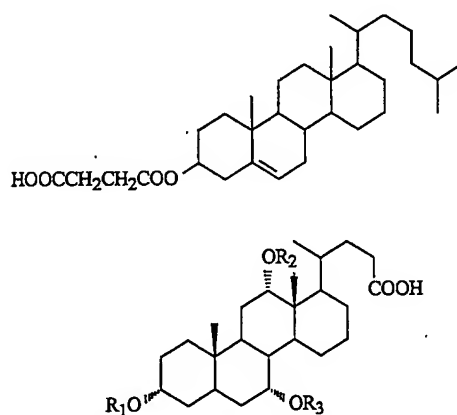


Vitamin D derivative

In yet further contemplated aspects, Levovirin prodrugs may be polymerized via a phosphate groups that couples the respective 2'- or 3'-hydroxyl group of the ribose with the 5'OH group of the next ribose. Exemplary structures are given below (wherein the nucleoside is in the L-configuration):



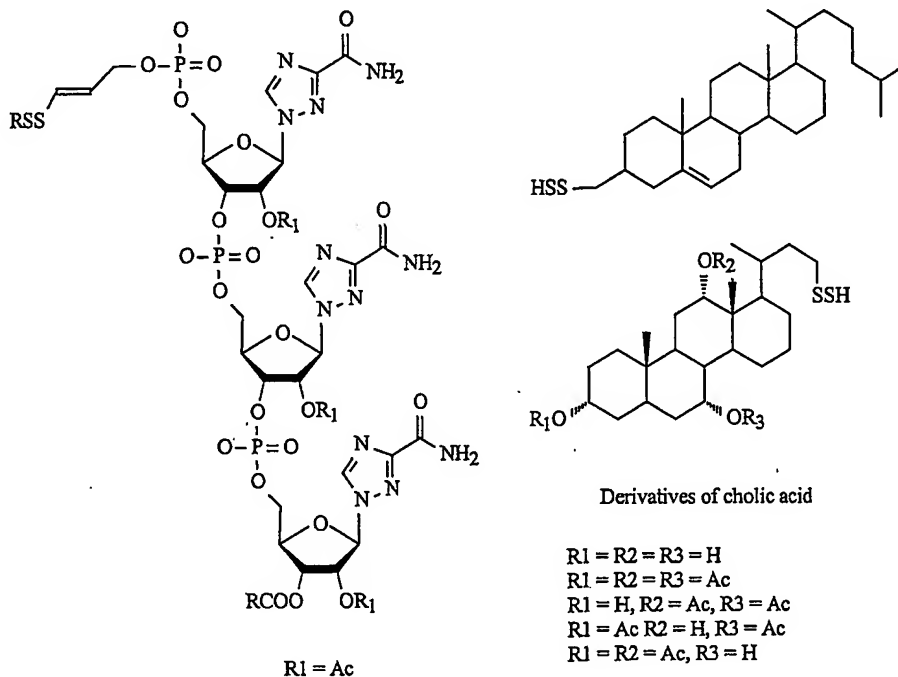
R₁ = Ac



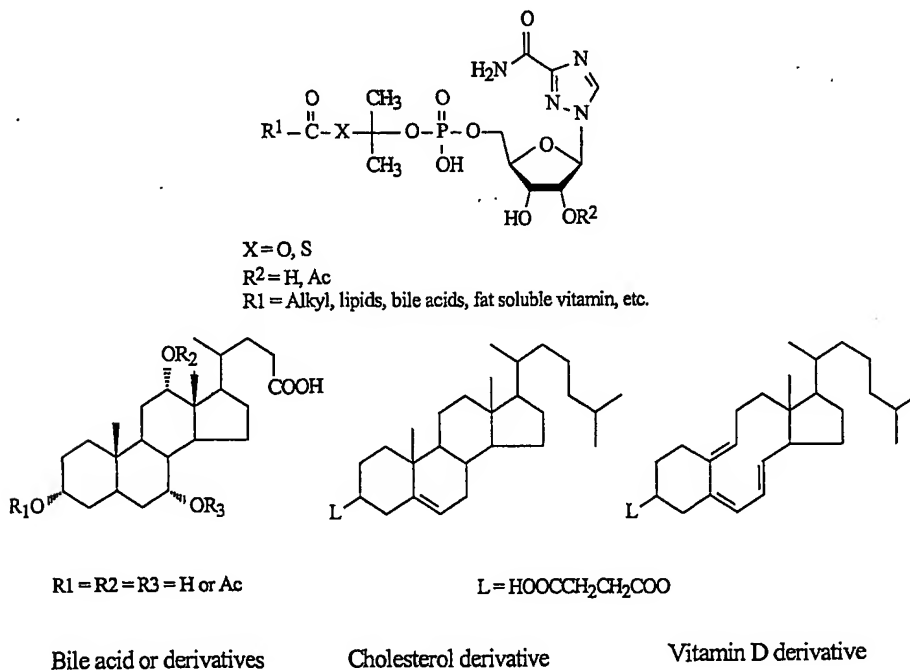
Derivatives of cholic acid

R₁ = R₂ = R₃ = H
 R₁ = R₂ = R₃ = Ac
 R₁ = H, R₂ = Ac, R₃ = Ac
 R₁ = Ac R₂ = H, R₃ = Ac
 R₁ = R₂ = Ac, R₃ = H

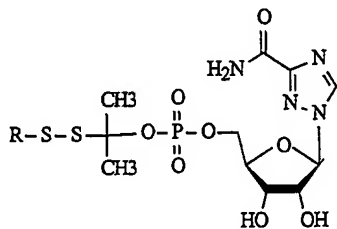
In a particularly contemplated aspect, the nucleoside analogs are coupled via a disulfide bond to a lipophilic moiety, and such exemplary prodrugs have a structure as depicted below (with Levovirin in the L-configuration):



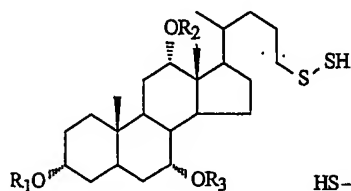
5 Still further contemplated Levovirin prodrugs include phosphate esters with lipophilic compounds as outlined below (with Levovirin in the L-configuration):



Where it is especially desirable that the lipophilic moiety is coupled to Levovirin via a disulfide bond, contemplated Levovirin prodrugs may have a structure as depicted below (with Levovirin in the L-configuration):

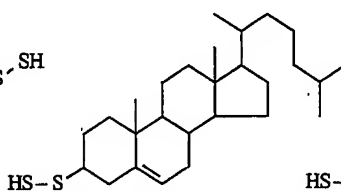


R = Alkyl, Cholesterol, Bile acid, Fat soluble vitamin, or other lipids

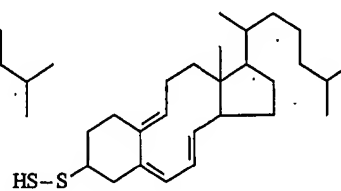


R₁ = R₂ = R₃ = H or Ac

Derivatives of cholic acid

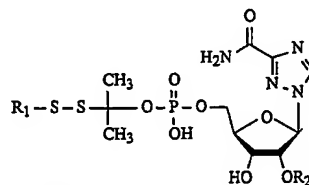


Cholesterol derivative



Vitamin D derivative

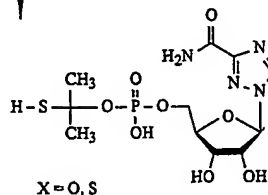
- 5 It is generally contemplated that bio-transformations for the above synthetic schemes may be applied to all contemplated nucleoside pro-drugs are as follows (with Levovirin in the L-configuration):



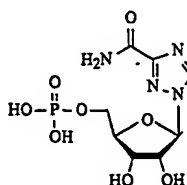
R₁ = Lipids, Alkyl, Bile acid,
R₂ = H, Ac

Glutathione

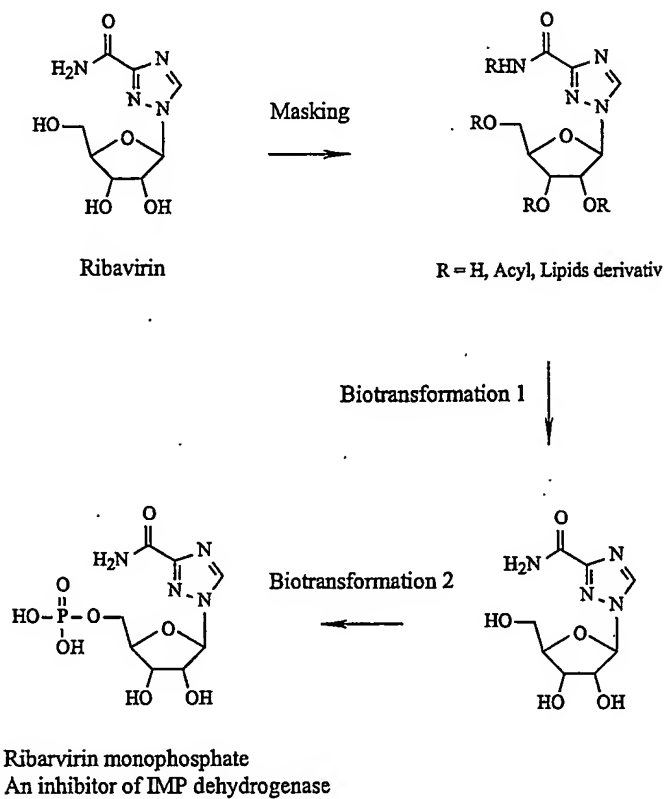
R₁-SH



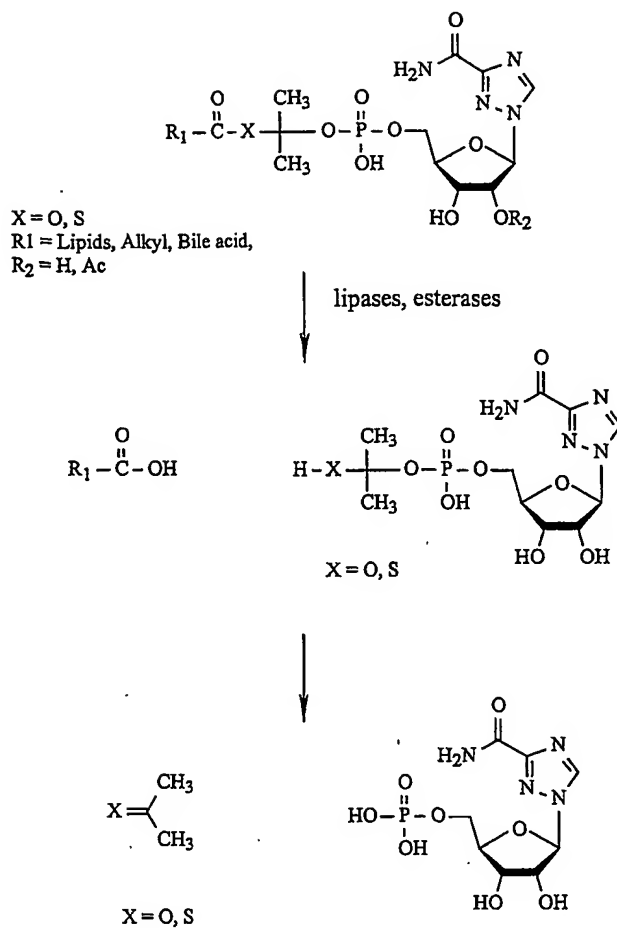
X = O, S



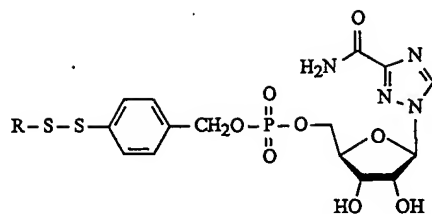
Alternatively, contemplated bio-transformations may follow the general scheme as outlined below (with Levovirin in the L-configuration):



In further alternative aspects, bio-transformations may be performed as follows:

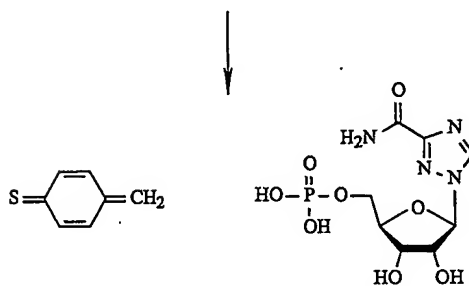
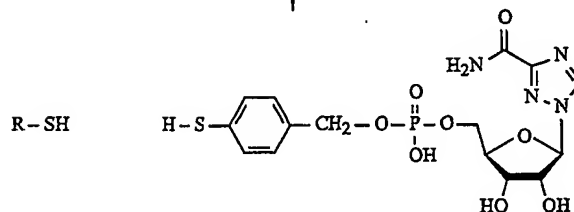


and in still further alternative aspects, the bio-transformation may be performed as shown below:

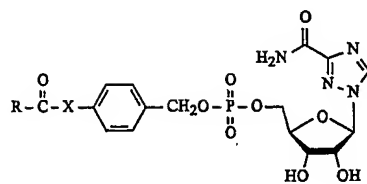


R = Alkyl, lipids, vitamin, bile acid, etc.

Glutathione, nonenzymatic



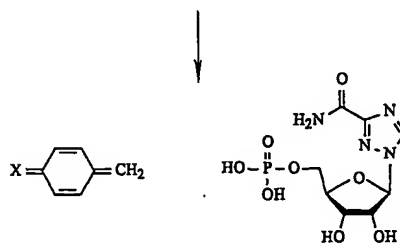
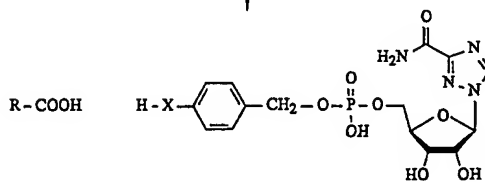
or:



X = O, S, NH

R = Alkyl, lipids, vitamin, bile acid, etc.

lipases, esterases



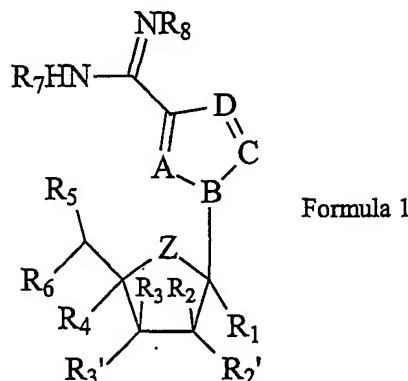
With respect to the synthesis of contemplated compounds comprising a diazole or modified diazole ring, it is contemplated that the synthetic procedure substantially follows a protocol as described for the synthesis of Ribavirin (*e.g.*, U.S. Pat. No. 3,798,209 to *Witkowski et al.* and U.S. Pat. No. 3,976,545 to *Witkowski et al.*) in which the triazole moiety is replaced
5 with a modified or unmodified diazole moiety.

Thus, specific embodiments and applications of nucleoside analog prodrugs have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit
10 of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms “comprises” and “comprising” should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components,
15 or steps that are not expressly referenced.

CLAIMS

We claim:

1. A nucleoside analog of Formula 1, in which the sugar is either in L- or D-configuration:



wherein A, C, and D are independently selected from N or C-R₉, and wherein R₉ is H, halogen, lower alkyl, alkenyl, alkynyl, amino, CN, SH, CHO, COOH, CH₂OH, vinyl halide or hydroxyl; B is N or C;

Z is O, CH₂, or S;

R₂' and R₃' are independently H, hydroxyl, protected hydroxyl, or halogen;

R₁, R₂, R₃, R₄, R₅, are independently H, halogen, CN, CH₂OH, lower alkyl, vinyl, or acetylene, with the proviso that when R₂ is hydroxyl, then R₂' is not halogen, and with the further proviso that when R₃ is hydroxyl, then R₃' is not halogen;

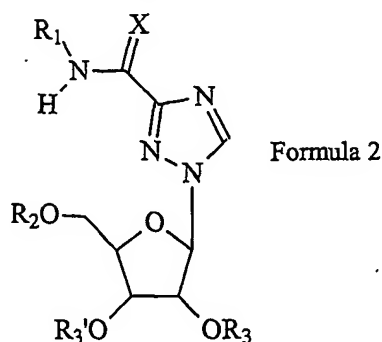
R₆ is H, hydroxyl, protected hydroxyl, -CH₂OH, -CH₂PO(OH)₂-, an O-amino acid, O-retinoic acid, O-cholesterol, O-cholic acid, O-coumarinic acid, O-salicylic acid, O-succinic acid, an O-bile acid, an O-lipid, O-P(O)-(O-CH₂-CH₂-S-CO-CH₃)₂, an O-steroid, an O-monophosphate derivative, an O-diphosphate derivative, or an O-triphosphate derivative;

R₇ is H, alkyl, CH₃COO-, CH₃COO-Phenyl-CH₂-O-CO-, phenyl, -(CH₂)_n-COOH, coumarinic acid, salicylic acid, a dithiosuccinoyl derivative, a reductase cleavable group, phosphonoformic acid, or a phosphoramidate group; and

R₈ is H, lower alkyl, phenyl, CH₃COO-, CH₃COO-Phenyl-CH₂-O-CO-, phenyl, or -(CH₂)_n-COOH; or

R₇ and R₈ combined are selected from a cyclic structure or an amino acid, with the further proviso that (i) when R₁, R₂, R₃, R₄, R₅, R₇, and R₈ are H, and when R₂' and R₃' are hydroxyl, then R₆ is not hydroxyl, and (ii) when R₁, R₂, R₃, R₄, R₅, and R₈ are H, and when R₂', R₃', and R₆ are hydroxyl, then R₇ is not H.

2. A nucleoside analog of Formula 2, in which the sugar is either in L- or D-configuration:



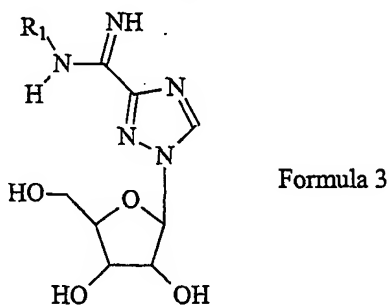
wherein X is O or NH;

R₁ is a masking group of the amino group;

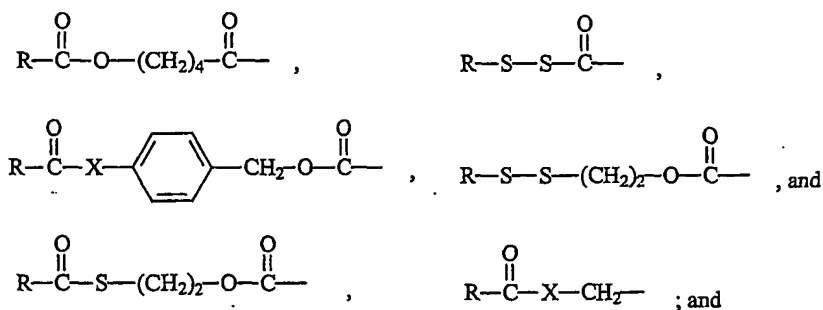
R₂ is H, -CHO-, -C(O)R, and -P(O)(OR')₂, where R is C₁-C₁₇ alkyl, alkenyl, or alkynyl, and R' is a masking group of the phosphate group; and

R₃ and R₃' are independently H or C₁-C₁₈ acyl, with the proviso that R₁ and R₂ are not hydrogen at the same time.

3. A nucleoside analog of Formula 3, in which the sugar is either in L- or D-configuration:

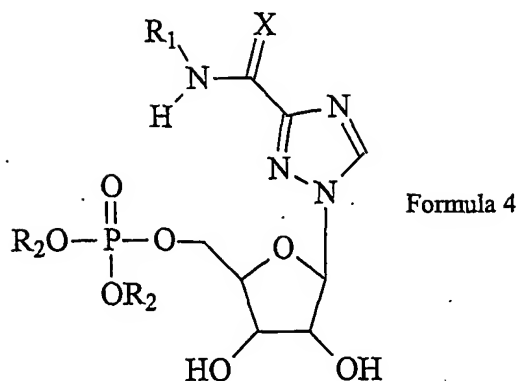


where R₁ is a masking group selected from the group consisting of:

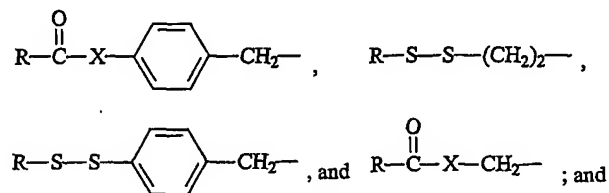


wherein X is O or S, and R is a C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl.

4. A nucleoside analog of Formula 4, in which the sugar is either in L- or D-configuration:

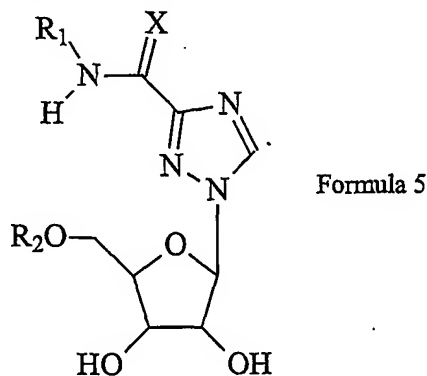


wherein R_1 is H or a masking group of the amino group, and wherein R_2 is a masking group of the phosphate selected from the group consisting of:

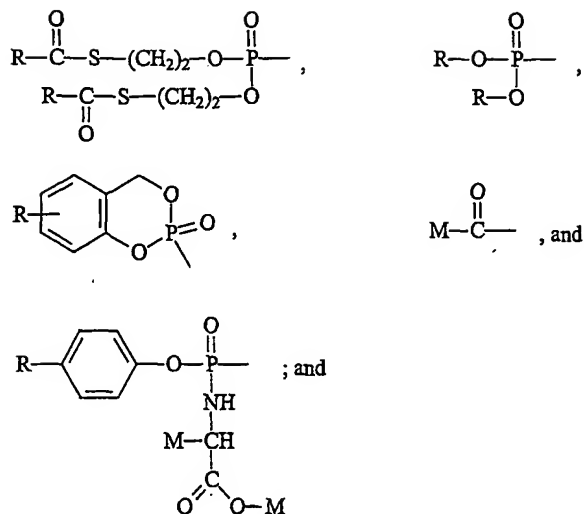


wherein X is O or S, and wherein R is C_1 - C_{18} alkyl, alkenyl, alkynyl, aryl, or aralkyl.

5. A nucleoside analog of Formula 5, in which the sugar is either in L- or D-configuration:

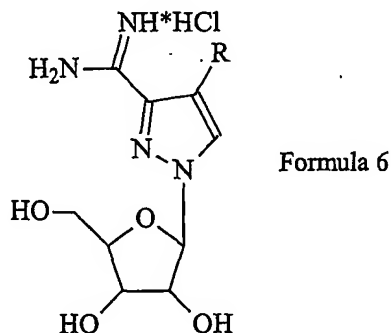


wherein R_1 is H or a masking group of the amino group; and R_2 is a group having a structure selected from the group consisting of:



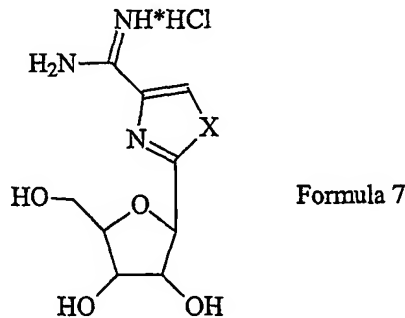
wherein R is C₁-C₁₈ alkyl, alkenyl, alkynyl, aryl, or aralkyl, and wherein M is alkyl, alkenyl, alkynyl, aralkyl, aryl, or a hydrophobic group.

6. A nucleoside analog of Formula 6, in which the sugar is either in the L- or D-configuration:



wherein R is hydrogen, hydroxyl, halogen, alkyl, phenyl, vinyl, acetylene, an amide, or an amidine.

7. A nucleoside analog of Formula 7, in which the sugar is either in L- or D- configuration:



wherein X is oxygen, sulphur, Se or NR, and wherein R is H, acetyl, or alkyl.

8. A method of treating a mammal having a viral infection comprising:

providing a pharmaceutical composition comprising a compound selected from the group consisting of a compound according to claim 1, a compound according to claim 2, a compound according to claim 3, a compound according to claim 4, a compound according to claim 5, a compound according to claim 6, and a compound according to claim 7; and
administering the pharmaceutical composition to the mammal.

9. The method of claim 8 wherein the pharmaceutical composition comprises a compound selected from the group consisting of a compound according to claim 1, a compound according to claim 2, and a compound according to claim 3.
10. The method of claim 8 wherein the pharmaceutical composition comprises a compound selected from the group consisting of a compound according to claim 4, a compound according to claim 5, a compound according to claim 6, and a compound according to claim 7.
11. The method of claim 8 wherein the viral infection comprises an infection with an HCV virus or an HBV virus, and wherein the mammal is a human.
12. A method of modulating a cytokine profile in a mammal comprising:
providing a pharmaceutical composition comprising a compound selected from the group consisting of a compound according to claim 1, a compound according to claim 2, a compound according to claim 3, a compound according to claim 4, a compound according to claim 5, a compound according to claim 6, and a compound according to claim 7; and
administering the pharmaceutical composition to the mammal in a dosage effective to reduce expression of a type 1 cytokine and stimulate expression of a Type 2 cytokine.
13. The method of claim 12 wherein the pharmaceutical composition comprises a compound selected from the group consisting of a compound according to claim 1, a compound according to claim 2, and a compound according to claim 3.
14. The method of claim 12 wherein the pharmaceutical composition comprises a compound selected from the group consisting of a compound according to claim 4, a compound

according to claim 5, a compound according to claim 6, and a compound according to claim 7.

15. The method of claim 12 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/08713

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 19/052, 19/056; A61K 31/70

US CL : 536/28.6, 28.7; 514/43

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/28.6, 28.7; 514/43

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US Re29,835 A (WITKOWSKI et al.) 14 November 1978(14.11.78), see entire document.	1-2, 6, 8-9, 12-13 and 15
X	US 3,798,209 A (WITKOWSKI et al.) 19 March 1974(19.03.74), see entire document.	1-2, 6, 8-9, 12-13 and 15
X	US 3,984,396 A (WITKOWSKI et al.) 05 October 1976(05.10.76), see entire document.	1-2, 6, 8-9, 12-13 and 15
X	US 3,991,078 A (WITKOWSKI et al.) 09 November 1976(09.11.76), see entire document.	1-2, 6, 8-9, 12-13 and 15
Y	JP 64-026593 A (ASAHI GLASS KK) 27 January 1989(27.01.89), see entire document.	6-7, 10-11 and 14-15

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

04 MAY 2001

Date of mailing of the international search report

09 JUL 2001

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/08713

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,093,624 A (REVANKAR et al.) 06 June 1978(06.06.78), see entire document.	1-15